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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/187,385	11/06/1998	SVETOMIR N. MARKOVIC	07039/119001	2986

26191 7590 01/28/2004

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EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/187,385	MARKOVIC, SVETOMIR N.	
	Examin r	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication app ars on the cover sheet with th correspondence address --

Period for R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-12,18,21,22,26,27 and 30-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-12,18,21,22,26,27 and 30-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The response filed Oct. 3, 2003 is acknowledged.

2. Claims 8-12, 18, 21, 22, 26, 27 and 30-38 are pending and examined on the merits.

3. The declaration of Svetomir N. Markovic, filed under 1.132, has been considered, but appears to be incomplete.

Claim Rejections Maintained:

4. The rejection of claims 26, 8-12, 18, 21, and 22 under 35 U.S.C. 103(a) as being unpatentable over Tovey et al (U.S. Patent 5,997,858; issued Dec. 7, 1999; filed May 9, 1997) in view of Brittenden et al (Brittenden, J. et al. Cancer, 77(7): 1226-1243, 1996, April) is maintained for the reasons of record.

Applicant has rebutted the rejection of the claims as unpatentable over Tovey in view of Brittenden by asserting the dosage ranges are critical to the operation of the claimed methods and bases this argument on evidence supplied in a declaration filed under 37 C.F.R. 1.132. However, upon review, the declaration appears to be incomplete because it refers to Figures 1-3, which are not found with the declaration. Therefore, the rejection is maintained for the reasons of record, because the declaration cannot be used to assess applicant's assertion concerning the criticality of the claimed dosage levels.

Additionally, applicant argues that the declaration provides evidence of the criticality of the claimed range, and this criticality may e used as a basis to rebut a prima facie case of

obviousness based on overlapping ranges. However, the data provided by the declaration is insufficient evidence that the claimed ranges are critical for the operation of the claimed methods. The data show that one data point, that in the middle of the range appears to be optimum, but fails to show that claimed range would produce unexpected results over the what is taught in the prior art. This is because the declaration fails to show any data for points outside the claimed range, with which to compare the data that is presented for the entire range.

Claim 26 is drawn to a method for stimulating the immune system of a human patient having a non-resectable malignant tumor, comprising administering alpha-interferon to said patient and treating said patient with non-surgical medical methodologies to diminish said tumor, wherein the dosage of alpha-interferon is about 250,000 U/m^2 to about 500,000 U/m^2 per day. Claim 8 limits claim 26 to a dosage that is administered once per day. Claims 9 and 11 recite that the dosage increases NK lymphocyte cytotoxicity at least 50 percent or 75 percent above NK lymphocyte cytotoxicity measured prior to administering alpha-interferon. Claims 10 and 12 recite that the NK lymphocyte toxicity is measured at effector to target cell ratios of 15:1 to 50:1. Claims 18, 21 and 22 limit the claimed methods to treatment of various cancers such as breast cancer, lung cancer, pancreatic cancer, brain cancer, prostate cancer, ovarian cancer, uterine cancer, renal cancer, and melanoma.

Tovey teaches methods of administering, oromucosally, alpha-interferon in comparable dosage ranges, 5000 U to about 20×10^6 U, with a preferable range of 1×10^4 U to about 1×10^6 U. Tovey teaches dosage ranges for alpha interferon in a 70 kg man (column 2, lines 25-38) and that the alpha interferon may be administered once per day (see claim 2). Tovey teaches treating renal cell carcinoma, malignant melanoma, lung cancer, and brain tumors (column 2, lines 4-16).

Tovey teaches a method where the interferon is administered in combination with chemotherapy or radiation therapy (column 2, lines 54-57). In addition, Tovey teaches that the mechanism for the beneficial effects of alpha-interferon may be due to stimulation of lymphoid tissue surrounding the nasopharyngeal and oral cavities. Thus, it appears that Tovey teaches immunostimulatory dosages.

Tovey uses different units to describe the dosages of alpha interferon. However, a comparison is readily made. Assuming an average 70kg man has about 1.86 m^2 suface area, the dosages recited in the claims are about 475,000 U/man to about 950,000 U/man. Thus, the narrowest range of Tovey encompasses the claimed range of dosages, where the highest dosages are almost the same. Thus, it appears that claimed methods recite a dosage range that is an optimization of the prior art range.

Tovey fails to teach a method comprising determining natural killer (NK) cell cytotoxicity. However, Brittendon teaches that alpha interferon enhances NK cell activity, and that NK cell activity plays an important role in natural cytotoxicity of cancer cells. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have added steps where natural kill lymphocyte cytotoxicity was measured before and after treatment to assess the patients ability to fight cancer.

Because Tovey teaches methods using dosages that are within the range of those recited in the instant claims, Tovey inherently teaches the methods of claims 9-12. Additionally, the ability of alpha-interferon to increase NK-lymphocyte activity is an inherent effect of the administration of alpha-interferon, as evidence by the teachings of Brittenden. Brittenden teaches alpha-interferon enhances NK cell activity and has been successfully used in the

treatment of renal carcinoma as part of a therapeutic regimen comprising the administration of interleukin-2 (see page 1234, 2nd column).

5. The rejection of claims 27 and 30-38 under 35 U.S.C. 103(a) as being unpatentable over Markovic et al[a] (Markovic, S.N. et al, Int. J. Cancer, 45: 788-794, 1990; IDS ref. "CH") in view of Tovey et al (U.S. Patent 5,997,858; issued Dec. 7, 1999; filed May 9, 1997) is maintained for the reasons of record.

Applicant has rebutted the rejection of the claims as unpatentable over Markovic in view of Tovey by asserting the the dosage ranges are critical to the operation of the claimed methods and bases this argument on evidence supplied in a declaration filed under 37 C.F.R. 1.132. However, upon review, the declaration appears to be incomplete because it refers to Figures 1-3, which are not found with the declaration. Therefore, the rejection is maintained for the reasons of record, because the declaration cannot be used to assess applicant's assertion concerning the criticality of the claimed dosage levels.

Additionally, applicant argues that the declaration provides evidence of the criticality of the claimed range, and this criticality may e used as a basis to rebut a prima facie case of obviousness based on overlapping ranges. However, the data provided by the declaration is insufficient evidence that the claimed ranges are critical for the operation of the claimed methods. The data show that one data point, that in the middle of the range appears to be optimum, but fails to show that claimed range would produce unexpected results over the what is taught in the prior art. This is because the declaration fails to show any data for points outside the claimed range, with which to compare the data that is presented for the entire range.

Claim 27 is drawn to a method for stimulating the immune system of a patient having a respectable tumor, comprising administering alpha-interferon to increasing the natural killer lymphocyte cytotoxicity by at least 50 percent above baseline; and surgically resecting the tumor. Dependent claims 30-38 add limitations to the schedule of interferon administration and to the measurement of NK lymphocyte cytotoxicity. Claim 35 limits the cancer to various cancers. Claim 33 limits the increase in NK lymphocyte cytotoxicity to at least 75 percent above baseline. Claims 32 and 34 recite effector to target cell ratios of NK lymphocytes.

Markovic teaches that alpha-interferon acts to increase NK lymphocyte cytotoxicity and that this is a desired effect in the surgical treatment of cancer because of the presence of disseminated tumor foci following surgical excision of the primary tumor. Markovic also teaches a method for the surgical removal of a tumor in mice, where the mice were treated prior to surgery with alpha interferon. Markovic fails to teach the method in humans and fails to teach the dosages necessary to increase NK lymphocyte cytotoxicity by at least 50 percent or 75 percent. However, Tovey teaches dosages in humans that stimulate the immune system, and Tovey's dosage ranges encompass the claimed dosage range. (Tovey uses different units to describe the dosages of alpha interferon. However, a comparison is readily made. Assuming an average 70kg man has about 1.86 m^2 suface area, the dosages recited in the claims are about 475,000 U/man to about 950,000 U/man. Thus, the narrowest range of Tovey encompasses the claimed range of dosages, where the highest dosages are almost the same.) Thus, it appears that claimed methods recite a dosage range that is an optimization of the prior art range.

Thus, it would have been prima facie obvious to one of skill in the art at the time the invention was made to have used the teachings of Markovic to make a method for treating

humans by combining the teachings of Markovic with the teachings of Tovey, because Markovic teaches that stimulation of the immune system is desirable after surgical removal of tumor.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran
Patent Examiner
January 12, 2004